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EXAMINER

GROSS, CHRISTOPHER M

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1639

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

The examiner charged with the present case has changed. See contact information below. Responsive to communications entered 4/13/2010. As of 4/13/2010, claims 40,45-53 are pending. Claims 40,45-53 are under consideration.

Priority

This application is filed under 35 U.S.C 371 of PCT/US03/37963 (filed on 11/26/2003), which claims priority as a CIP of US patent application 10/306,614 (filed on 11/26/2002).

Withdrawn Objection(s) and/or Rejection(s)

The provisional rejection of Claims 14, 16, 22-24, 26, 28 and 31 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48, 60, 62, 64 and 66 of copending Application No. 10/306,614 (PGPUB 20040101822; referred to as '614) is hereby withdrawn in view of the abandonment of '614.

The rejection of claims **14, 16, 17, 22, 23, 25, 26, 28-32 and 34-38** under **35 U.S.C. 102(e)** as being anticipated by **Trau** et al (PGPUB 20030124564; 7/3/2003; filed 7/1/02 or earlier priority date 6/29/01) is hereby withdrawn in view of applicant's cancellation of the claims.

The rejection of claims **14, 16, 17, 22, 23, 25, 26, 28-32 and 34-44** under 35 U.S.C. 103(a) as being unpatentable over **Trau** et al (PGPUB 20030124564; 7/3/2003; filed 7/1/02 or earlier priority date 6/29/01) and in view of **van Blaaderen** et al. (The Colloid Chemistry of Silica. Chapter 4, pp.84-111; Advances in Chemistry. Vol.234;

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1994) is hereby withdrawn in view of applicant's amendments or cancellation of the claims.

The rejection of claims **14, 16, 17, 22, 23, 25, 26** and **28-44** under 35 U.S.C. 103(a) as being unpatentable over **Trau** et al (PGPUB 20030124564; 7/3/2003; filed 7/1/02 or earlier priority date 6/29/01) and in view of **van Blaaderen** et al. (The Colloid Chemistry of Silica. Chapter 4, pp.84-111; Advances in Chemistry. Vol.234; 1994) as applied to claims 14, 16, 17, 22, 23, 25, 26, 28-32 and 34-44, and further in view of **Gu** et al. (PGPUB 20020048800; 4/25/2002; cited previously) is hereby withdrawn in view of applicant's amendments or cancellation of the claims.

The rejection referred to as "Claims **14, 16, 17, 22, 23, 25, 26** and **28-44** are rejected under **35 U.S.C. 102(e)** as being 35 U.S.C. 103(a) as being unpatentable over **van Blaaderen** et al. (Langmuir. Vol.8: 2921-2931; 1992; cited in IDS; referred to as van Blaaderen (92)), in view of **van Blaaderen** et al. (The Colloid Chemistry of Silica. Chapter 4, pp.84-111; Advances in Chemistry. Vol.234; 1994; referred to as van Blaaderen (94)), **Gu** et al. (PGPUB 20020048800; 4/25/2002; cited previously) and **Melde** et al. (Chem. Mater. Vol.11: 3302-3308; 1999)" as set forth in the last office action pp 14-19 is hereby withdrawn upon further consideration, however the references may or may not be used as part of a future rejection.

Information Disclosure Statement

The information disclosure statement filed 2/28/2006 is objected for failing to comply with 37 CFR 1.98(a)(5) with regard to citation nos. A-F and H because they do

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not include either the Journal Name plus Volume (Publisher) or else the publication date. Appropriate corrections are required.

New Claim Rejection(s) – Necessitated by Amendment

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40,45-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Battersby et al** (WO 00/32542) in view of **Ichinose et al** (1993 Chemistry Letters pp 1961-1964).

The present invention is drawn to a fluorescent silica-based nanoparticle comprising:

a silica-based core comprising an[d] organic functional group comprising a mercapto substituent group;

an organic fluorescent compound positioned within the silica-based core; and

a silica shell surrounding at least a portion of the core,

wherein the fluorescent silica-based nanoparticle has a diameter of 70 nm or less and is conjugated to a ligand.

For the purposes of this rejection, "a silica-based core comprising and organic functional group comprising a mercapto substituent" of claim 40 line 3 is interpreted as one organic functional group bearing a thiol (i.e.-RSH) . See 35 USC 112 second paragraph rejection below.

Battersby et al teach, throughout the document and especially the abstract, example 3 pp 39-42 fluorescently labeled silica microspheres for encoded solid-phase synthesis.

More specifically on p 39, figure 7 and p 42 first full paragraph Battersby et al teach 2-3 nm and smaller silica seed crystals which may be derivatized with aminopropyl silane (APS) followed by fluorescein isothiocyanate (FITC) and follow procedure of van Blaaderen et al (1992 Langmuir 8:2921-2931 – IDS entry 2/28/2006) for seed growth (shell formation) to make labeled silica microspheres. Said seed crystals are taken as "a silica-based core comprising an organic functional group" of claim 40 and overlaps the core radii of claims 52 and 53. Said FITC reads on "an

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organic fluorescent compound positioned within the silica-based core” of claim 40 and covalent attachment of 49. Battersby et al further teach on pp 39-40 that stable sols of 10-130 nm were possible, overlapping the 70 and 50 or less nm range set forth in claims 40 and 45, especially in view of figure 1C of the present application, indicating the claimed nanoparticles may be homogeneous. Alternatively, on p 40, based upon formula 3.1, Battersby et al disclose particle growth (i.e. any shell diameter) may be chosen based on concentrations of water, TEOS and ammonia. As mentioned above and evidenced by figure 1 of van Blaaderen, said seed growth procedure provides silica shells, as set forth in claim 40 and cover 100 % of the core surface area core, as set forth in claim 48. Battersby et al suggest on p 25-26 the microspheres may be used synthesize peptide ligands thereon via immobilization of carboxylic acids through amine (-NH₂) anchors (e.g. forming a C-terminal amide), reading on the ligand conjugate of claim 40, the peptide or oligopeptide of claim 46 as well as the amide of claim 47.

On p 26, Battersby et al also envision protein ligands, further reading on claim 46.

Battersby et al do not teach mercapto (thiol) substituents, as set forth in claim 40 or maleimides of claim 51.

Ichinose et al teach, throughout the document and especially structure 2 on p 1962 top left and the first full paragraph on p 1962, derivatization of glass with 3-mercaptopropyltrimethoxysilane (MPS) followed by reaction with a N-(1-pyrenyl)maleimide (MPI) thereto, providing the functional group comprising a mercapto substituent group of claim 40 as well as the maleimide of claim 51.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to derivatize the seed silica cores of Battersby et al with MPS for reaction with a maleimide according to Ichinose et al.

With regard to claim 50, drawn to the quantum yield of the fluorescent dye being about 2-3 times greater than free in aqueous solution, in accordance with MPEP 2112.01, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, **the applicant has the burden of showing that they are not.**” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Emphasis added

Therein, absent evidence to the contrary, the PTO has sound basis for believing that the microspheres of Battersby et al appear identical and/or are produced by a substantially identical process, thus would inherently double or triple the quantum efficiency of, for instance, FITC according to Battersby et al or MPI according to Ichinose et al. Notably in this regard, as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith.” *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

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One of ordinary skill in the art would have been motivated to derivatize the seed silica cores of Battersby et al with MPS for reaction with a maleimide according to Ichinose et al because (i) silane mediated thiol (mercaptan) immobilization is directly applicable toward modifying microdomains (i.e. such as microbead cores), as explicitly stated by Ichinose et al on p 1964 last paragraph and (ii) the mercapto group is a versatile and key functional group in protein chemistry, which may be converted to other functional groups through alkylating agents (such as MPI, a fluorescent label), as noted by Ichinose et al on p 1961 first full paragraph of the text. Furthermore, in accordance with In accordance with MPEP 2141 section III and *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385,1395 (2007), simple substitution of one known element (APS + FITC of Battersby et al) for another (MPS + MPI of Ichinose et al) to obtain predictable results is obvious.

One of ordinary skill in the art would have had a reasonable expectation of success in using MPS and MPI on glass of Ichinose et al for the labeling silica core microdomains per Battersby et al because the chemistry is quite similar, as glass constitutes a type of silica, thus the method of Ichinose et al falls squarely in the scope of technology of Battersby et al.

In conclusion, the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and was as a whole, prima facie obvious.

35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection concerns “new matter.”

The specification as originally filed provided no implicit or explicit support for ligands including proteins, peptides or oligopeptides, as set forth in new claim 46 or linkages including esters, thiolesters, amides or sulfate esters, as set forth in claim 47.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the disclosure. See MPEP 714.02, paragraph 5, last sentence and also MPEP 2163.06 I.

MPEP 2163.06 notes “If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition

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to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40,45-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 recites vague and indefinite language in lines 3-4 which recites "a silica-based core comprising and organic functional group comprising a mercapto substituent". It is not clear if this refers to one (an) organic functional group comprising a mercapto substituent (a.k.a. thiol) versus, perhaps, another unrecited organic functional group and/or multiple substituents, as suggested by "and"

In accordance with MPEP 2173.02: If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph, would be appropriate. See *Morton Int 'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

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As currently written, the metes and bounds of the claims are unascertainable. Therefore, claim 40 and all dependent claims are rejected under 35 USC 112, second paragraph.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571 272 0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross
Examiner
Art Unit 1639

cg

/ Christopher S. F. Low /
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